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 ORIGINAL REFERENCE NO.: 72:16437a,16440a  
 TITLE: Anthelmintic 5-substituted aminobenzimidazoles  
 INVENTOR(S): Hoff, Dale R.; Fisher, Michael Herbert  
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CA 967962			CA	
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US 3646049		19720229	US	19700305
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GI For diagram(s), see printed CA Issue.

AB The title compds. (I) are anthelmintics, particularly useful in treating veterinary nematode infections (given orally) and also possess antifungal properties. To a solution of 10 g II (R1 = H, R2 = 4-thiazolyl) in 20 ml concentrated H2SO4 was added dropwise at 20-30° a mixture of 4 ml concentrated HNO3 and 6 ml concentrated H2SO4, and the mixture kept 5 min to give II (R1 =

O2N, R2 = 4-thiazolyl) (III), m. 240-1° (HCONMe2) (DMF). A solution of 2.2 g furfural in 3 ml EtOH was added to 3 g 3,4-(H2N)2C6H3-NO2 (IV) suspended in 10 ml PhNO2, and the mixture stirred 10 min at room temperature then heated slowly to 210° 1 min (allowing the EtOH to dist.) to give II (R1 = O2N, R2 = 2-furyl), m. 224°. II (R1 = O2N, R2 = 2-pyrrolyl), m.

259-60° was prepared by refluxing a mixture of 43.2 g 2-formylpyrrole, 54 g IV, and 160 g Cu(OAc)2 in 1 l. MeOH 2 hr. Catalytic hydrogenation of 141 g III in 4 l. EtOH over 22 g 5% Pd-C at 24° and 45 psi 5.5 hr gave II (R1 = H2N, R2 = 4-thiazolyl) (V), m. 232-3° (EtOH-Hexane).

Addition of 1 g ClCO2Me to a suspension of 2.16 g V in 7.5 ml C5H5N gave II (R1 = MeO2CNH, R2 = 4-thiazolyl) (Va), m. 237-9° (MeOH containing C), also obtained in the absence of C5H5N using Me2CO as solvent at room

temperature

Similarly were prepared the following II (R2 = 4-thiazolyl) (R1 and m.p. given): EtO2CNH, 203-5° (MeCN-Et2O) (methanolate m.

94-105°); PrO2CNH, 214-15°; BuO2CNH, 211-12°; C5H11O2CNH, 178-9°; C6H13O2CNH, 150-2°; n-C8H17O2CNH, 66-7°; PhO2CNH, 115-16°; 4-FC6H4O2CNH, 275-80°; 2-FC6H4O2CNH, 135-40°; iso-BuO2CNH, 231-2°; Me2CHO2CNH, 212-14°; CH2:CHCH2O2CNH, 210-12°; HC.tplbond.CCH2O2CNH,

200-2°; EtSC(O)NH, 215°; and cyclopropyloxycarbonylamino, 190-5° (hydrate), 207-8° (anhydrous). By standard acylation procedures were prepared the following I (R1 = H, X = O), (R2 and m.p. given): Me, 280°; PhCH2, 210-11°; H, 247-8°; Et, 255-6°; Ph (VI), 118-20°; 3-pyridyl, 284-5°; 2-FC6H4, 132-3°; 1-adamantyl, 246-7°; 2-naphthyl, 154-6°; cyclopropyl, 245°; Me2CH, 203-5°; 3-thienyl, 276-8°; 3-FC6H4, 232-3°; 4-FC6H4, 151-2°; 2-MeOC6H4, 113-14°; 3-MeOC6H4, 105-9°; 2-PhO, 95-100°; 2-ClC6H4, 146-7°; 3-IC6H4, 127-9°; 3-F3CC6H4, 201-3°; 3-O2NC6H4, 163-4°; 2,5-F2C6H3, 113-14°; 2-pyridyl, 240-1°; 4-pyridyl, 150-3°; Me3C, 241-2°; 2-furyl, 139-40°; 4-thiazolyl, 387-8°; 2-thienyl, 288° (decomposition); MeOCH2, 238-9°; Cl2CH, 220°; and Me2C:CH, 270-2°. Refluxing a mixture of 5 g I (R1 = H, R2 = EtS, X = O), (VIa) 0.5 g Bu2SnO, and 50 ml F3CCH2OH 20 hr gave I (R1 = H, R2 = F3CCH2O), m. 231-2° (AcOEt-hexane). I (R1 = H, R2 = HC.tplbond.CCH2O, X = O), m. 202-2°, was similarly prepared. Addition of 3.62 g PhOC(S)Cl dropwise to 4.32 g V in 25 ml C5H5N and stirring 1.5 hr gave I (R1 = H, R2 = PhO, X = S), m. 155-7° (MeOH), which on heating in C5H5N (7 vols.) 1 hr at 100° gave 5-isothiocyanato-2-(4-thiazolyl)benzimidazole (VII), m. 243-6°. I (R1 = H, R2 = MeO, X = S), m. 224° (MeOH), was prepared by refluxing a mixture of 2.5 g VII, 25 mg NaOMe, and 300 ml MeOH 20 hr; I (R1 = H, R2 = EtO, X = S), prepared similarly, m. 218°. A slow stream of MeSH was passed into 4 g VII in 25 ml Me2NCHO 15 min, and the mixture kept 20 hr to give I (R1 = H, R2 = MeS, X = S), m. 202-5°. I (R1 = H, R2 = Ph, X = S), m. 140-3° (MeOH), was obtained by refluxing a mixture of 1 g VI, 2 g P2S5, and 20 ml C5H5N 25 min. A suspension of V (amount unspecified) in 25 ml C5H5N was treated dropwise with 1.2 g MeNCO and the mixture stirred 2.5 hr to give I (R1 = H, R2 = MeNH, X = O), m. 160° (MeOH). Dropwise addition of 2.5 g Me2NCOC1 to a suspension of 4.32 g V in 25 ml C5H5N gave I (R1 = H, R2 = Me2N, X = O), m. 260-2° (MeOH). Refluxing a mixture of 5 g VIa and 25 ml Et2NH 6 hr gave I (R1 = H, R2 = Et2N, X = O), m. 234-5°. The following I (R1 = H) were similarly prepared (R2, X, and m.p.given): pyrrolidino, O, 296-8°; piperidino, O, -; MeNH, S, 235-7°; PhNH, S, 244-6°; Me2N, S, 156-9°; Et2N, S, 130-5°; piperidino, S, 225-6°, and pyrrolidino, S, 257-8°. A mixture of 8.5 g I (R1 = H, R2 = Me2CHO, X = O) (VIII), 100 ml DMF and 2.3 g 52% NaOH emulsion in mineral oil was stirred at room temperature 20 min., heated 10 min at 50°, cooled to room temperature, treated with 7.1 g MeI in 10 ml DMF, and the mixture heated 20 min at 80° to give I (R1 = Me, R2 = Me2CHO, X = O), purified by crystallization from AcOEt. Addition of a mixture of 1.3 ml concentrated HNO3 (d. 1.41) and 2.8 ml concentrated H2SO4 to 3.8 g 1-methoxy-2-(4-thiazolyl)benzimidazole in 12.3 ml concentrated H2SO4 at 12° gave 1.5 g 5-nitro-1-methoxy-2-(4-thiazolyl)benzimidazole (IX). m. 220-1° (MeOH). Hydrogenation of IX in MeOH and treatment with methanolic HCl gave 450 mg amorphous 5-amino analog-HCl, which with ClCO2CHMe2 in C5H5N gave I (R1 = MeO, R2 = Me2CHO, X = O), m. 123-5°. Treatment of 5.4 g Va in 100 ml PhMe and 30 ml DMF with 0.7 g NaH in 2 ml PhMe at 65°, stirring 1 hr, adding 2.5 g AcCl at 55°, and refluxing 0.5 hr gave I (R1 = Ac, R2 = MeO, X = O). A mixture of 3.26 g VIII and 1 g BuNCO in 100 ml MeCN was refluxed 4 hr to give I (R1 = BuNHCO, R2 =

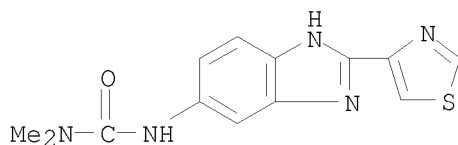
Me<sub>2</sub>CHO, X = O). Treatment of VIII in C<sub>5</sub>H<sub>5</sub>N with ClCO<sub>2</sub>CHMe<sub>2</sub> gave I (R<sub>1</sub> = Me<sub>2</sub>CHO<sub>2</sub>C, R<sub>2</sub> = Me<sub>2</sub>CHO, X = O), crystallized from aqueous MeOH. Similarly, V and MeSO<sub>2</sub>Cl gave II (R<sub>1</sub> = MeSO<sub>2</sub>NH, R<sub>2</sub> = 4-thiazolyl), m. 225-6° (MeOH). II (R<sub>1</sub> = PhSO<sub>2</sub>NH, R<sub>2</sub> = 4-thiazolyl) (X), m. 254-5°, was also prepared. Methylation of 3.5 g X in 10 ml MeOH containing 0.54 g NaOMe with 0.625 ml MeI gave II (R<sub>1</sub> PhSO<sub>2</sub>NMe, R<sub>2</sub> = 4-thiazolyl), m. 142-3° (MeOH); II (R<sub>1</sub> = MeSO<sub>2</sub>NMe, R<sub>2</sub> = 4-thiazolyl), m. 192-3° (MeCN), was also prepared. The following XI were analogously prepared (R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and m.p. given): H, MeO<sub>2</sub>CNMe, 4-thiazolyl, 161-2°; H, MeO<sub>2</sub>CNH, 2-furyl, 162-3°; MeO, MeO<sub>2</sub>CNH, 2-furyl, 164°; H, EtO<sub>2</sub>CNH, 2-furyl, 171-2°; H, PhO<sub>2</sub>CNH, 2-furyl, 150-5°; H, EtO<sub>2</sub>CNH, 2-pyrrolyl, 200-2°; H, MeO<sub>2</sub>CNH, 2-thienyl, 185-8°; H, MeO<sub>2</sub>CNH, 1,2,5-thiadiazol-3-yl, 150-5°; H, MeO<sub>2</sub>CNH, 1-pyrazolyl, 207-10°; H, MeO<sub>2</sub>CNH, 2-methyl-4-thiazolyl, 135°; H, MeO<sub>2</sub>CNH, 1,2,3-thiadiazol-4-yl, 218-20°; H, MeO<sub>2</sub>CNH, 1,3,4-thiadiazol-2-yl, 258°; H, Me<sub>2</sub>CHO<sub>2</sub>CNH, 2-oxazolyl, 206°; H, Me<sub>2</sub>CHO<sub>2</sub>CNH, 2-thiazolyl, 234°; H, MeO<sub>2</sub>CNH, 2-imidazolyl, 205-7°; H, 4-FC<sub>6</sub>H<sub>4</sub>CONH, 2-furyl, 264°; H, 2-furoylamino, 2-furyl, 248°; H, 4-FC<sub>6</sub>H<sub>4</sub>CONH, 1-pyrazolyl, 230°; H, BzNH, 2-thiazolyl, 135-40°.

IT 27217-07-8P 27217-08-9P 27217-09-0P  
28767-12-6P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of)

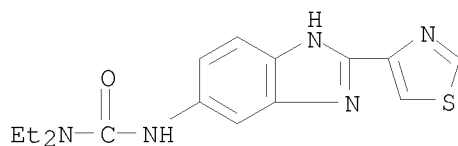
RN 27217-07-8 CAPLUS

CN Urea, N,N-dimethyl-N'-[2-(4-thiazolyl)-1H-benzimidazol-5-yl]- (9CI) (CA INDEX NAME)



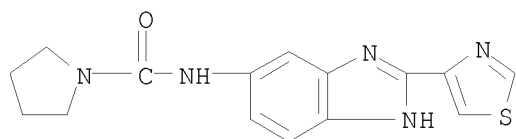
RN 27217-08-9 CAPLUS

CN Urea, 1,1-diethyl-3-[2-(4-thiazolyl)-5-benzimidazolyl]- (8CI) (CA INDEX NAME)



RN 27217-09-0 CAPLUS

CN 1-Pyrrolidinecarboxamide, N-[2-(4-thiazolyl)-5-benzimidazolyl]- (8CI) (CA INDEX NAME)



RN 28767-12-6 CAPLUS

CN Urea, 1-methyl-3-[2-(4-thiazolyl)-5-benzimidazolyl]- (8CI) (CA INDEX  
NAME)

